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Chapter 3

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Renal Pharmacology

Ebrahim S. Behairy

Part 1: Some Physiology and Pathophysiology

Tubular function and urine formation

- The renal blood flow (RBF) is 1.1 L/min (~ 22% of COP).
- The glomerular filtration rate (GFR) is 125 ml/min.
- The capillary tuft filtrates ~ 180 L of fluid per day. 99% of the filtered fluid is reabsorbed again during passage in the renal tubules.
- Water reabsorption is usually 2ry to Na⁺ reabsorption (except in the collecting tubules; 'CT'). Any drug that ↓ Na⁺ reabsorption (= ↑ Na⁺ loss), also ↓ water reabsorption (= ↑ water loss of 'diuresis').

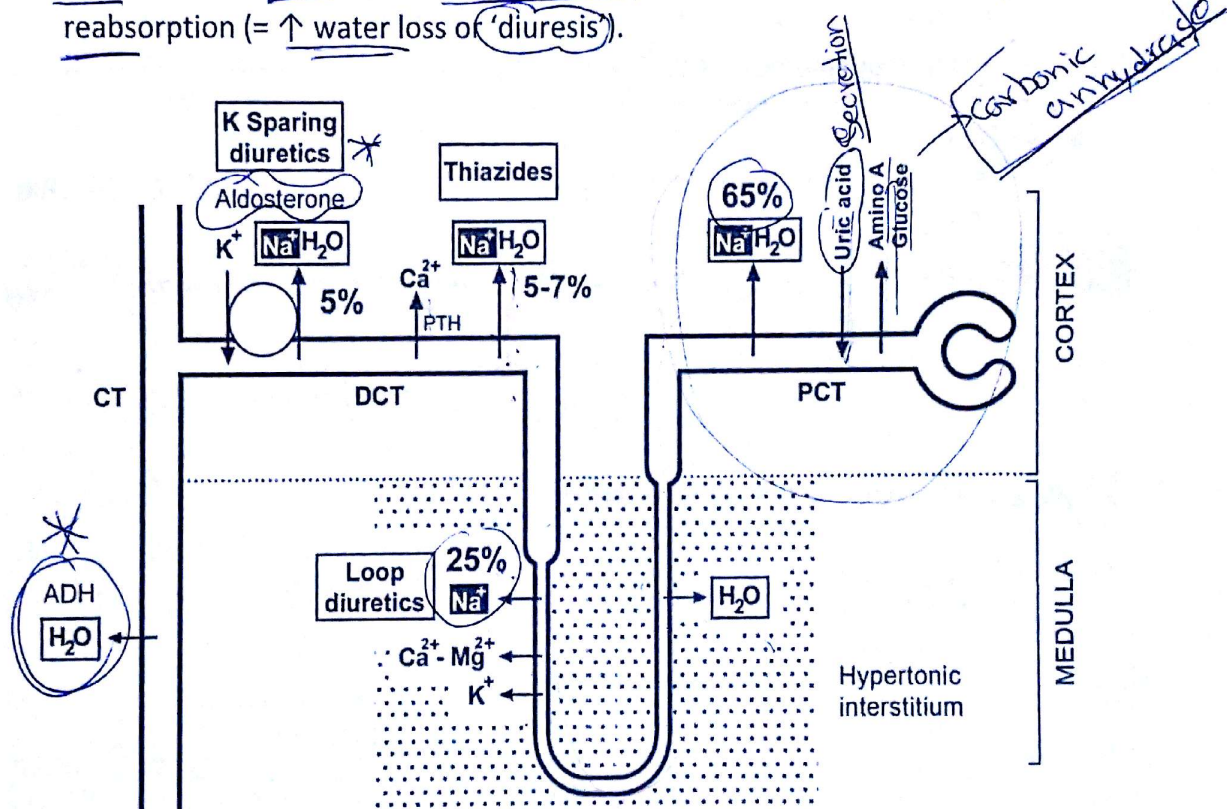


Fig 1. Tubular reabsorption and sites of action of 3 types of diuretics

Proximal convoluted tubules (PCT):

- Reabsorption: (75% of the glomerular filtrate).
 - Active reabsorption of Na⁺ (~65%).
 - Passive (2ry to Na⁺) reabsorption of equiosmotic amount of water.

- Reabsorption of all filtered K^+ glucose, amino acids, and drugs.
- Secretion: active secretion and reabsorption of organic acids and bases into tubular fluid.

Loop of Henle (LOH):

- Descending limb: passive reabsorption of water due to hypertonicity of the medullary interstitium.
- Ascending limb: active reabsorption of Na^+ (~25%) (this causes hypertonicity of the medullary interstitium), Ca^{2+} and Mg^{2+} .

Distal convoluted tubules (DCT):

- Proximal part:
 - Active reabsorption of Na^+ (5-7%).
 - Passive (2ry to Na^+) reabsorption of equiosmotic amount of water.
 - Active reabsorption of Ca^{2+} (under the influence of parathormone 'PTH').
- Distal part:
 - Active reabsorption of Na^+ (2-5%) in exchange with K^+ (under the influence of aldosterone).
 - Passive (2ry to Na^+) reabsorption of equiosmotic amount of water.

Collecting tubules (CT): Reabsorption of water under the influence of ADH.

Edema and edematous conditions

- Edema is defined as the accumulation of fluid in the interstitial space due to either:
 - Increased capillary hydrostatic pressure ✓
 - Decreased plasma oncotic pressure.
 - Increased capillary permeability.
- ✓ ■ Edema can be either exudative (having high protein content) or transudative (having low protein content).
- Exudative edema results from increased capillary permeability as part of the acute inflammatory response. It is usually localized to the site of inflammation and will not be considered in this chapter.
- Transudative edema is usually generalized and is associated with renal Na^+ retention. The three most common clinical causes are:

- **Congestive heart failure (CHF)**: the decreased COP causes renal ischemia which stimulates the renin-angiotensin-aldosterone system (RAAS) → Na^+ and water retention → edema.
- **Liver cirrhosis**: the cirrhotic liver cannot synthesize sufficient albumin and other plasma proteins → ↓ plasma oncotic pressure. Hypoalbuminemia + together with portal hypertension and 2ry stimulation of RAAS cause fluid retention (edema) and accumulation of fluid in the peritoneal cavity (ascites).
- **Nephrotic syndrome**: glomerular dysfunction causes excessive loss of plasma proteins in urine → ↓ plasma oncotic pressure → edema.

Part 2: Diuretic classes and agents

Diuretics are drugs that increase urine volume and Na^+ excretion.

Natriuretic: a drug that increase Na^+ excretion by the kidney.

Classification of diuretics:

Renal diuretics

They act directly on the kidney:

- **Thiazide diuretics**: act on the proximal part of the DCT e.g. hydrochlorothiazide.
- **Loop diuretics**: act on the ascending limb of loop of Henle e.g. furosemide.
- **K^+ sparing diuretics**: act on the distal part of the DCT e.g. spironolactone.
- **Osmotic diuretics**: substances that ↑ the osmotic pressure of tubular fluid → ↓ water reabsorption by renal tubules e.g. mannitol.

Extra-renal diuretics

They act indirectly on the kidney:

- **Water diuresis**: ↑ water intake → ↓ ADH release → diuresis.
- **Digitalis in CHF**: ↑ the COP leading to ↑ RBF → diuresis.
- **i.v. albumin in ascites or nephrotic edema**: to increase plasma osmotic pressure → mobilization of edema fluid toward the vascular compartment → ↑ RBF → diuresis.

N.B. Carbonic anhydrase inhibitors e.g. acetazolamide: they are weak diuretics that ↓ NaHCO_3 reabsorption from the PCT and may cause mild metabolic acidosis.

* They also $\downarrow$ aqueous humor secretion and can be used in the treatment of glaucoma (see pharmacology of the eye).

■ **Loop diuretics** ($\text{Na}^+/\text{K}^+/\text{2Cl}^-$ symport inhibitor, high ceiling diuretic)
(Furosemide, Torsemide, bumetanide, and ethacrynic acid)

Pharmacokinetics *Sulphonamide derivatives*

منشأها من مشتقات السلفوناميد

- They are absorbed from the GIT and secreted into the lumen of the PCT by an organic acid excretory system.
- Diuresis occurs within 5 minutes of i.v. administration and within 30 minutes of oral administration.

Mechanism and pharmacological effects

① Loop diuretics inhibit $\text{Na}^+/\text{K}^+/\text{2Cl}^-$ co-transport system in the thick ascending limb of LOH leading to inhibition of the active reabsorption Na^+ , Cl^- , and K^+ . These ions are excreted with equiosmotic amount of water.

- They also increase excretion of Ca^{2+} , Mg^{2+} , halides and H^+
- Na^+ and water loss at this segment is high, so they are potent (or high ceiling) diuretics (i.e., up to 25% of the filtered Na^+ load).

② They $\uparrow$ renal PGE2 and PGI2 production leading to VD and $\uparrow$ RBF and GFR.

- Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit PG synthesis and antagonize this effect of loop diuretics.
- VD of pulmonary vascular bed also occurs due to $\uparrow$ PG formation.

Therapeutic uses

■ **Edematous conditions:** e.g. CHF, nephrotic syndrome, etc.

- Drinking excess water causes return of edema; many patients require fluid and salt restriction to have the best results.
- Diuretics are not used to treat edema due to lymphatic obstruction (lymphedema) or inflammatory edema (localized edema with high protein content is difficult to be resolved by diuretics).

■ **Acute pulmonary edema:** loop diuretic $\downarrow$ pulmonary congestion by:

- They cause venodilatation $\rightarrow$ $\downarrow$ venous return.
- They cause VD of pulmonary vascular bed even before diuresis occurs.

■ **Acute renal failure:** to maintain adequate GFR and enhance K^+ excretion.

(i.v. preferred)

Miner → 1 endolymph

- Acute hypercalcemia and acute hyperkalemia: saline should be given to compensate for Na^+ and water loss.

- Hypertensive emergencies: i.v. furosemide is usually given in emergencies:

renal ↓ Loop diuretics ↓ plasma volume.

They cause peripheral VD due to ↑ PGs production in many vascular beds.

The hyponatremia decreases sensitivity of the vascular endothelium to circulating catecholamines.

□ Anion overdose

Adverse effects

- Hypovolemia and hypotension.

- Electrolyte disturbances: Hyponatremia, hypokalemia, hypomagnesemia, and hypocalcemia (all need to be properly replaced).

- Hypokalemic metabolic alkalosis: due to ↑ tubular secretion of K^+ and H^+ .

- Hyperuricemia and precipitation of acute gout: This is caused by:

- Increased uric acid reabsorption in the PCT caused by hypovolemia (It may be prevented by using lower doses to avoid hypovolemia).
- Competition with uric acid excretion at the organic acid excretory system in the PCT.

- Ototoxicity:

- It is reversible hearing loss. It occurs with very high doses.
- It may be due to impairment of ion transport in the stria vascularis (inner ear).
- Occurs more frequent with:
 - Patients with impaired renal function.
 - Ethacrynic acid.
 - Concomitant use of other ototoxic drugs e.g. aminoglycosides.

- Allergic reactions: all loop diuretics (except ethacrynic acid) are derivatives of sulfonamides they cause occasional skin rash, eosinophilia, and less often, interstitial nephritis.

Notes

restriction to therapeutic use of loop diuretics

- * renal insufficiency
- * hyperglycemia
- * liver cirrhosis
- * heart failure
- * medical emergency
- * allergic
- * borderline renal failure

Contraindication:

■ Thiazide diuretics (Na-Cl symport inhibitor)

- **True thiazides** (derivatives of **sulfonamides**): **chlorothiazide**, **hydrochlorothiazide**.
- **Thiazide-like diuretics**: **metolazone**, **indapamide**, **chlorthalidone**.
 ↓
 biliary secretion

Pharmacokinetics

- Thiazide diuretics are absorbed from the GIT. They are secreted into the lumen of the PCT by an organic acid excretory system.
- They produce diuresis within 1-2 hours.

Mechanism and pharmacological effects

- Thiazides inhibit Na^+/Cl^- co-transport system in the proximal part of DCT leading to inhibition of the active reabsorption Na^+ , Cl^- . These ions are excreted with equiosmotic amount of water.
 - Excess Na^+ reaching the DCT is reabsorbed in exchange with K^+ ($\rightarrow$ K^+ loss).
 - They also increase excretion of halides and H^+ .
 - They $\downarrow$ Ca^{2+} excretion and enhance its reabsorption.
 - Thiazides have moderate efficacy (i.e., maximum excretion of filtered Na^+ load is only 5-7%).
 - Most thiazides are ineffective if the GFR is $< 30-40$ ml/min (so it is not useful, or even harmful, in presence of renal failure)*
- The action of thiazides also depends on renal PGs (like loop diuretics).

Therapeutic doses

- **Mild edematous states:** cardiac, hepatic, or renal (same as loop diuretics).
- **Essential hypertension** (mild to moderate): diuretics , VD
 - 1, 2, 3 - They have the same mechanisms like loop diuretics (mention them).
 - 2, 3 - They are often combined with other antihypertensive drugs to enhance their blood pressure-lowering effects.
- * ■ **Hypercalcuria and renal Ca^{2+} stones:** to ↓ urinary Ca^{2+} excretion.
- * ■ **Nephrogenic diabetes insipidus (DI):**
 - Thiazides can reduce urine volume in some cases of DI. This is called "paradoxical antidiuretic action" and it is not clearly understood. It may be due to improvement of ADH receptor sensitivity in the renal collecting tubules.

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Adverse effects

- **Hypovolemia and hypotension.**
- **Electrolyte disturbances:** Hyponatremia and hypokalemia. *no meq no Ca*
- **Hypokalemic metabolic alkalosis:** due to $\uparrow$ tubular secretion of K^+ and H^+ .
- **Hyperuricemia** the same as with loop diuretics. *hypovolemia competition*
- * ■ **Hyperglycemia:** due to both $\downarrow$ pancreatic release of insulin and $\downarrow$ tissue utilization of glucose. *met*
- * ■ **Hyperlipidemia:** due to $\uparrow$ cholesterol and LDL (by 5-15%).
- ✓ ■ **Allergic reactions:** thiazides are derivatives of sulfonamides; they cause occasional skin rash, dermatitis, and less often, thrombocytopenia. *DE*

* **hypercalcaemia**

impotence

Potassium-sparing diuretics

* **(Spironolactone) (triamterene) (amiloride)**

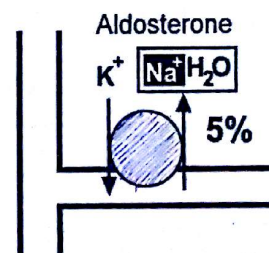
- Spironolactone is a **steroid congener of aldosterone**.
- Triamterene and amiloride are synthetic drugs but **not steroids**. *

Pharmacokinetics

- ✓ ■ All are absorbed from the GIT.
- Spironolactone and triamterene are metabolized by the liver.
- Amiloride is **excreted unchanged in the urine**.
- They have **slow onset** (days).

Mechanism and pharmacological effects

- **Site of action:** the **distal part of the DCT** where Na^+ is reabsorbed (2-5%) in exchange with K^+ under the influence of **aldosterone**.
- Spironolactone is a **competitive antagonist** of aldosterone at its receptor site at the distal part of DCT leading to $\uparrow Na^+$ excretion (with excretion of equiosmotic amount of water) and K^+ retention.
- Triamterene and amiloride are **direct inhibitors of Na^+ channels** in the distal part of DCT leading to $\uparrow Na^+$ excretion (with excretion of equiosmotic amount of water) and K^+ retention.



■ The net effects are:

- Mild Na^+ and water loss (i.e., maximum excretion of filtered Na^+ is only 2-5%)
- * - Hyperkalemia: due to $\downarrow$ K^+ excretion (K^+ will be retained in blood).
- * - Metabolic acidosis: due to $\downarrow$ H^+ ion excretion (H^+ will be retained in blood).

Therapeutic uses

■ All cases of edema due to hyperaldosteronism:

- Primary hyperaldosteronism: e.g. Conn's disease
- Secondary hyperaldosteronism: e.g. in liver cirrhosis or nephrotic syndrome.

■ Used in combination with loop diuretics or thiazides in order to:

- To minimize the risk of electrolyte imbalance:
Loop diuretics cause hypokalemia while K^+ sparing diuretics cause hyperkalemia. Their combination can minimize electrolyte disturbance.
- To minimize the risk of acid-base imbalance:
Loop diuretics cause metabolic alkalosis while K^+ sparing diuretics cause metabolic acidosis. Their combination can minimize acid-base imbalance.
- To make synergism in cases of refractory (resistant) edema.

■ Treatment of female pattern hair loss:

Spironolactone is a weak competitive inhibitor of androgens at their receptors and $\downarrow$ synthesis of testosterone (antiandrogenic effect). Some dermatologists use this feature to stop androgen-related frontal hair loss in women.

Side effects

✓ Hyperkalemia due to $\downarrow$ K^+ excretion.

✓ Hyperkalemic metabolic acidosis: due to $\downarrow$ K^+ and $\downarrow$ H^+ excretion.

- Spironolactone has antiandrogenic effects (gynecomastia and impotence in males).

* N.B. Eplerenone (similar congener of spironolactone) has little antiandrogenic effects but more hyperkalemic effects.

Notes Spironolactone, triamterene, amiloride, Eplerenone

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Contraindications:

- All cases of hyperkalemia: especially in the following conditions:
 - Patients with chronic renal failure.
 - With drugs that cause hyperkalemia (e.g. ACEIs, β -blockers, NSAIDs).
- Spironolactone should not be given with carbenoxolone because carbenoxolone has aldosterone-like action $\rightarrow$ antagonize the effect of spironolactone.

	Spironolactone	Triamterene - amiloride
Structure	<u>Synthetic steroid</u>	<u>Synthetic non-steroids</u>
Metabolism	<u>Extensive metabolism in the liver</u>	<u>Amiloride is excreted unchanged</u>
Mechanism of action	<u>Competitive antagonism with aldosterone at its receptor site in the DCT</u>	<u>Direct inhibition of Na^+ channels at the distal part of DCT</u>
Antiandrogenic effects	<u>Gynecomastia & impotence</u>	<u>Not present</u>

■ Osmotic diuretics: Mannitol, Glycerol

They are chemically inert substances given by i.v. infusion in emergency conditions

Mechanism of action

- First, they $\uparrow$ osmotic pressure of plasma leading to withdrawal of transcellular fluid (e.g. aqueous humor, excessive CSF, etc).
- Second, they are freely filtered by the glomerulus and $\uparrow$ osmotic pr of the tubular fluid leading to $\downarrow$ active Na^+ and water reabsorption by renal tubules.

Therapeutic uses

Acute congestive glaucoma and acute rise in intracranial pressure: they are given for rapid $\uparrow$ drainage of aqueous humor or CSF respectively by increasing the osmotic pressure of the plasma before diuresis begins.

Side effects

Dehydration is the main side effect

Comparison between the 3 main classes of diuretics

	Loop diuretics	Thiazides	K ⁺ sparing diuretics
Site of action	thick ascending limb of LOH	proximal part of DCT	distal part of DCT
Mechanism	Inhibit Na ⁺ /K ⁺ /2Cl ⁻ co-transport system	inhibit Na ⁺ /Cl ⁻ co-transport system	Spironolactone is a competitive antagonist of aldosterone Triamterene and amiloride are direct inhibitors of Na ⁺ channels in the distal part of DCT
Efficacy	High	Moderate	Mild
Onset	Rapid (minutes)	Less rapid (hours)	Slow (days)
Serum K ⁺	Hypokalemia	Hypokalemia	Hyperkalemia
Blood pH	Metabolic alkalosis	Metabolic alkalosis	Metabolic acidosis
Ca ²⁺ excretion	↑	↓	↓
Use in renal failure	* Can be used	Not effective or harmful	Contraindicated → hyperkalemia
Use in hypertension	Hypertensive emergencies	Mild essential hypertension	In combination with other diuretics
Blood glucose	Little or no effect	* Rise	Little or no effect
Plasma lipids	Little or no effect	* Rise	Little or no effect
Ototoxicity	* Common	Less common	Rare

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Part 3:

Clinical remarks on the use of diuretics in some edematous conditions

Congestive heart failure (CHF):

This patient has weak cardiac muscle ($\downarrow$ COP), salt & water retention, and lung congestion.

Advantages of diuretics:

- Correction of salt & water retention. ✓
- To decrease preload (venodilatation and $\downarrow$ venous return) and afterload (due to arterial VD) $\rightarrow$ improvement of cardiac function.
- To decrease lung congestion $\rightarrow$ improvement of tissue oxygenation.

Disadvantages of diuretics:

- Excessive hypovolemia can $\downarrow$ COP.
- Diuretic-induced acid-base imbalance may impair cardiac function.
- Diuretic-induced hypokalemia can $\uparrow$ digitalis toxicity and predispose to cardiac arrhythmia.

Combination between a K^+ sparing diuretic + loop diuretic is the best choice.

Chronic kidney diseases:

The majority of patients with chronic renal diseases (e.g. chronic RF, diabetic nephropathy, etc.) have salt & water retention, hyperkalemia, and hypertension.

Advantages of diuretics:

- Correction of salt & water retention. ✓
- Correction of hyperkalemia. ✓
- Reduction of hypertension. ✓

Loop diuretics are best choice.

Disadvantages of diuretics:

- Thiazides are ineffective when GFR is <30 ml/min, moreover it may be harmful.
- K^+ sparing diuretics are contraindicated because they produce hyperkalemia.

Liver cirrhosis:

Patients with chronic liver disease have edema, ascites, hyperammonemia and 2ry hyperaldosteronism.

Advantages of diuretics:

- Correction of edema and ascites.

Disadvantages of diuretics:

- * Vigorous diuresis can precipitate hyperammonemia and hepatorenal syndrome.
- * Electrolyte and acid base disturbances are dangerous in those patients.

K⁺ sparing diuretics are best choice because they don't cause excessive diuresis and they have anti-aldosterone effect.

Diuretic use during pregnancy:

Diuretics are better avoided in pregnancy because they effectively reduce maternal plasma volume and consequently decrease placental blood flow.

Notes

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Review Questions

Mention the pharmacodynamic principles underlying the use of:

- Furosemide in arterial hypertension.
- Furosemide in acute pulmonary edema.
- Thiazides in diabetes insipidus.

Mention the pharmacodynamic principles underlying the contraindication of:

- Furosemide in acute hyperuricemia.
- Thiazides in uncontrolled diabetes mellitus.
- Spironolactone in chronic renal failure.
- Amiloride with ACEIs.
- Ethacrynic acid with aminoglycosides.
- Furosemide with NSAIDs.

Mention the advantages and disadvantages of diuretics in the following conditions:

- Congestive heart failure.
- Chronic kidney disease.
- Chronic liver disease.

Mention the rational of the following combination:

- Furosemide with amiloride.

Mention 3 differences between:

- Furosemide and spironolactone.



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